UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/228,639	01/12/99	WESTON S	07164.0008

HM22/1013

FINNEGAN HENDERSON FARABOW
GARRETT AND DUNNER
1300 I STREET NW
WASHINGTON DC 20005

EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	13

DATE MAILED: 10/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/228,639	Applicant(s) WESTON ET AL.	
	Examiner Jeanine A Enewold Goldberg	Art Unit 1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *18 September 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5 and 12-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

1. This action is in response to the papers filed September 18, 2000. Currently, claims 1-3, 5, 12-18 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

2. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-3, 5, 10-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Little et al (EPO 497527A1, August 5, 1992) and Ferrie et al (Am. J. Human Genetic, Vol. 51, pg. 251-262, 1992) in view of Estivill et al (Human Mutation, Vol. 10, pg. 135-154, 1997) and CFGAC (Cystic Fibrosis Genetic Analysis Consortium, Human Mutation, Vol 4, pg. 167-177, 1994)

Little et al. (herein referred to as Little) teaches a method for detecting single nucleotide variations in the cystic fibrosis gene by amplification refractory mutation system (ARMS). The ARMS method includes treating the sample with nucleoside triphosphates, an agent for polymerization and a diagnostic primer. Moreover, Little teaches that ARMS is able to selectively amplify multiple sites to obtain multiple

amplification products to be distinguished simply, accurately, and with minimal operator skill thus providing a robust technique for screening a single sample for multiple nucleotide variations (pg. 2, lines 47-50). Little teaches numerous primers for ARMS analysis of the cystic fibrosis gene (pg. 27-29). Primers for 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H mutations are provided. The instant primers of SEQ ID NO: 12, 16, 17, 18 are identical to the Little primers 1879, 1880, 1879, 2072, respectively. Little teaches an ARMS reaction in which G542X, F508(M), 621+1 G>A, G551D mutations are multiplexed and analyzed.

Ferrie et al. (herein referred to as Ferrie) teaches the development of a multiplex ARMS test for common mutations in the CFTR gene. Ferrie teaches that ARMS systems have numerous advantages over other PCR-based systems including rapid, reliable, nonisotopic, and easily obtained results (pg. 251-252). Ferrie teaches that in principle, ARMS tests can be developed for any mutation. Ferrie teaches that ARMS tests have been developed for the following CFTR mutations: 1717-1G>A, G542X, W1282X, N1303K, F508(M), 621+1 G>A, R553X, G551D, and R117H. Moreover, Ferrie teaches how to increase sensitivity and design an ARMS system which would provide the ordinary artisan with the tools needed to optimize a reaction for a specific need. Ferrie teaches altering the primer sequence has a large effect on the yield and specificity of an individuals reaction within the multiplex, while small changes were obtained by altering the primer concentrations (pg. 258, col. 1). Further, Ferrie teaches that the yield of the primer pair was affected by the rate of hybridization of ARMS primer to the target DNA and the rate at which the bases at the 3' end of the AMRS primer

form a suitable substrate for Taq DNA polymerases (pg. 259, col. 2). Modification of the 3' sequence can change the specificity without significantly altering the calculated melting temperature (pg. 259, col. 2). Specificity may also be obtained by additional stabilization in which the choice of mismatched based was determined experimentally, given that purine/purine mismatches or pyrimidine/pyrimidine mismatches showed greater destabilization (pg. 259, col. 2). Also, specificity may be obtained by reducing the primer concentration and inclusion of control PCR reactions (pg. 259, col. 2). Ferrie also cites other references which discuss improving specificity by reducing the concentration of dNTP in the reaction (pg. 259, col. 2). Long primers (30 mers) ensured false priming events were minimized and that primer template interactions were stabilized and minimizing the disruptive effect of DNA polymorphisms (pg. 260, col. 1). Yields of the reaction needed to be relatively similar. Finally, ARMS multiplex has proved extremely reliable and has made the greatest impact on the speed of delivery of results (pg. 260, col. 2).

Neither Little nor Ferrie specifically teach the combination of primers for all of the recited mutations.

However, Estivill et al. (herein referred to as Estivill) teaches geographic distribution and regional origin of 272 cystic fibrosis mutations in European populations. There mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. G542X, W1282X, N1303K, F508(M), G551D are taught to be the most common mutations. Furthermore, all of 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T,

621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations are common in more than one region (Table 2 and 3).

Furthermore, CGFAC teaches that 24 of the most common mutations include 1717-1G>A, G542X, W1282X, N1303K, F508(M), 3849+ 10kb C>T, 621+1 G>A, R553X, G551D, R117H, R1162X and R334W mutations. The specific frequencies in which these mutations are found are provided.

Therefore, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Little, Ferrie in view of Estivill and CGFAC to obtain the invention as a whole. Little teaches primers for ARMS reactions to determine mutations in the CTFR gene. Ferrie teaches the modifications needed to be made to perform ARMS multiplex analysis. The ordinary artisan would have been able to have performed routine experimentation to optimize the ARMS systems desired for the particular situation. Further, all of the claimed mutations were known at the time the invention were made, as exemplified by Estivill and CFGAC. Further Estivill and CFGAC taught the relative frequencies of the mutations in numerous populations. Thus, the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC. Thus, based upon the general knowledge at the time the invention was made, the ordinary artisan would have been motivated to have made the invention as a whole.

Since Estivill and CFGAC provides the frequencies of CFTR mutations, Ferrie teaches the ordinary artisan how to optimize multiplex ARMS reactions, and Little teaches ARMS reactions are appropriate for determining single mutations in the CFTR, it would have been obvious to have designed a multiplex reaction which suited the individual needs of the artisan as all such modification would have produced functional equivalent results based upon the teachings of Little and Ferrie.

Further, it would have been **prima facie** obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Little with the teachings of Ferrie. Also, since the sequence of the CFTR gene was known, mutations within the CFTR were known, as taught by Estivill and CFGAC, generating primers for these regions would have been obvious over the teachings of Little and Ferrie which teach the properties of the primers needed for the ARMS assay. The ordinary artisan would have been motivated to determine whether the mutation was present in a sample using the multiplex ARMS method of Ferrie since the ARMS method is rapid, reliable and nonisotopic. The ordinary artisan would have further been motivated to have optimized primer selection to obtain optimal results for the ARMS reaction, based upon the teachings of Ferrie. Further, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, however, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For

example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent structural homologues of the full length disclosed nucleic acid sequence of the CFTR gene concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited reference in the absence of secondary considerations.

Response to Arguments

The response traverses the rejection. The response asserts that the mere fact that references can be modified does not render the resulting combination obvious unless the art suggest desirability of the combination, such that there was no motivation to have combined these references. This argument has been reviewed but is not convincing because as previously stated the ordinary artisan would have been motivated to either have selected certain mutations to screen for which were more probable in the specific individual being studied. Or, the ordinary artisan would have been motivated to screen for a more generic set of mutations which were relatively probable in all different populations based upon the teachings of Little and Ferrie in view of Estivill and CFGAC. Moreover, Ferrie teaches that for many diseases, there is more than one mutation responsible for the condition such that it makes mutation analysis more complex, and clearly a system which could simultaneously analyze a sample for the presence of multiple mutations would be useful.

Secondly, the response asserts that Ferrie teaches away from a test which uses more than the four primer sets in his inventions. This argument has been reviewed but is not convincing because Ferrie does not teach the practical limits. In the quote cited in the response that more than four primer sets is taught away from, "there are practical limits on the number which can routinely be performed", Ferrie does not teach what the practical limits are, but is rather teaching that studying all 150 mutations in a multiplex is out of the practical limits (pg. 252, col. 1). Additionally in response to applicant's arguments that multiplexing of more than four primer sets is taught away from based upon the practical limits, Schumm et al (US Pat. 5,843,660, December 1998) teaches the multiplexing of eight STR loci (example number 19). Further, Schumm teaches that successful combinations can be generated by trial and error of locus combinations, by selection of primer pair sequences, and by adjustment of primer concentrations to identify an equilibrium in which all included loci may be amplified. Thus, the art has taught the multiplexing of eight different loci in a single reaction vessel and thus, six primer sets of the instant invention is well within the realm of practical limits.

Thirdly, the response also asserts that the difficulty in multiplexing primers directed to four mutations as taught by Ferrie, as evidenced by the teachings on pg. 260, the teachings that some primers failed to yield a detectable product and the modification required to concentrations of primers to reach a balance. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an

appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the unpredictability must be supported by evidence, not argument. While the response argues that multiplexing requires analyzing the complexity of the interactions between the primers to achieve a successful system, this argument has been reviewed but is not convincing because the teachings of Ferrie not only point out potential difficulties with multiplexing of primers for detection of mutations, but also provide guidance to the ordinary artisan how to overcome these difficulties through routine experimentation. Ferrie teaches that altering the primer sequence had a large effect on the yield and specificity of an individual reaction within the multiples, altering primer concentrations has small changes (pg. 258, col. 1), and the use of longer primers (pg. 260, col. 1) are among the variables that Ferrie teaches to alter to obtain optimal results.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

4. No claims allowable over the art.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold
October 2, 2000

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600